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Parkinsonism in *FMR1* premutation carriers may be indistinguishable from Parkinson disease

Deborah A. Hall^{a,*}, Katherine Howard^a, Randi Hagerman^b, and Maureen A. Leehey^a

^a Department of Neurology, University of Colorado at Denver and Health Sciences Center, Denver, CO, United States

^b M.I.N.D. Institute and Department of Pediatrics, University of California at Davis Medical Center, Sacramento, CA, United States

Abstract

Premutation carriers of repeat expansions in the *fragile X mental retardation (FMR1)* gene develop kinetic tremor and ataxia or the ‘fragile X associated tremor/ataxia syndrome’ (FXTAS). Affected *FMR1* premutation carriers also have parkinsonism, but have not been reported to meet criteria for Parkinson disease. This case series illustrates that some patients who are *FMR1* premutation carriers may appear by history and examination to have idiopathic Parkinson disease. Based on previous studies, it is likely that the genetic mutation and parkinsonism are associated. Although screening all PD patients is likely to be low yield, genetic testing of *FMR1* in individuals with PD and a family history of fragile X syndrome, autism or developmental delay, or other related *FMR1* phenotypes is warranted.

Keywords

Parkinsonism; Fragile X mental retardation gene; Fragile X associated tremor/ataxia syndrome; Parkinson disease

1. Introduction

Movement disorders have been described in premutation carriers of the fragile X mental retardation (*FMR1*) gene. Most commonly, *FMR1* premutation carriers over the age of 55 have kinetic tremor and gait ataxia, otherwise known as the fragile X associated tremor/ataxia syndrome (FXTAS) [1]. Parkinsonism has also been reported in FXTAS, but most patients lack the characteristic resting tremor, cogwheel rigidity, and postural instability seen in idiopathic Parkinson disease (PD) [2]. As screening for *FMR1* mutations has become more widespread, the phenotype associated with a *FMR1* premutation range mutation has expanded. Although the premutation is not typically associated with a pure PD phenotype, some carriers do have many features classic for idiopathic PD. This paper describes four patients with the *FMR1* premutation who meet criteria for idiopathic PD [3]. This finding is important because patients with a PD phenotype and a family history consistent with *FMR1* related disease may warrant screening for the *FMR1* premutation.

*Corresponding author. Department of Neurology, University of Colorado at Denver and Health Sciences Center, Academic Office 1, 12631 E. 17th Avenue, Room 5113E, Aurora, CO 80045, USA. Tel./fax: +1 303 724 2122. E-mail address: E-mail: deborah.hall@uchsc.edu (D.A. Hall).

2. Report of cases

Cases were seen as part of a *FMRI* neurological phenotype study or an ongoing neuroepidemiology screening study for *FMRI* mutations in a movement disorder population. Both studies were approved by the Colorado Institutional Review Board and all patients signed a consent form prior to entry of the study.

2.1. Case 1

A 46-year-old right handed man presented with a one-year history of rest tremor in the right hand, with arm pain and stiffness. The patient reported numbness in his fingers and toes, slowed movement, and fatigue. He also described intermittent depression, electrical shock sensations in the left arm, and bladder over-activity. He had no family history of fragile X syndrome or developmental disorders. Examination showed normal eye movements and rigidity in the upper extremities with a rest tremor in the hands. The patient had decrement and decreased amplitude with finger tapping, hand opening and closing, which was worse on the right, and pronation supination hand maneuvers. Decreased arm swing on the right was present and gait was otherwise normal. Brain MRI was normal. Early-onset idiopathic PD was diagnosed and selegiline 5 mg twice daily was started. One year later, the patient reported worsening of his speech and difficulty walking through doorways, especially when crossing thresholds. This progressed to freezing spells, with dragging and shuffling of his feet. He began having angry outbursts and some forgetfulness of daily activities. Changes to his exam included the presence of a masked facial expression and increased tone in the head and neck region. He had slowed gait initiation and decreased stride length. He took three steps to turn. Unified Parkinson Disease Rating Scale (UPDRS) [4] motor score was 11 and his mental state exam was normal. Age 48, pramipexole was started and escalated to 1.5 mg per day with improvement in tremor and balance. The pramipexole was effective for 6–8 weeks but then tremors worsened. After increasing the dose, he reported tremor resolution and improved balance. His *FMRI* repeat size was 60.

2.2. Case 2

An 86-year-old right handed woman had onset of rest tremor in her left hand 10 years prior. Her medical history was remarkable for macular degeneration, osteoarthritis, urinary incontinence, and osteoporosis. Her pedigree is in Fig. 1A. On examination, she had bradykinesia, rigidity, and a 4 Hz rest tremor in the left hand. She had no postural instability or gait abnormality. She was diagnosed with PD at age 78 by a movement disorder specialist and started on selegiline and carbidopa/levodopa. She had a moderate improvement of her bradykinesia and near resolution of her tremor. At age 81, she began falling occasionally and developed stooped posture, with shuffling and cogwheel rigidity. Her carbidopa/levodopa was increased with subsequent improvement in her gait, bradykinesia, and rigidity. Over the next three years, she developed dementia with deficits on examination in orientation to date, following complex commands, and immediate and short term recall. She wandered at night without recollection and had developed hallucinations, seeing people in her room. Laboratory workup for dementia was negative including comprehensive metabolic panel, complete blood count, vitamin B12, folate, VDRL, and TSH. CT of the brain was normal and a brain MRI was not done. At age 84, she was wheelchair bound and unresponsive to carbidopa/levodopa. She was frequently confused and disoriented. At the age of 87, she was bed bound. Her mental status examination was 6/26, with correct responses in following commands, orientation questions, and tasks of attention. She had a grasp sign. She also had masked facies and increased tone in all extremities, but no tremor. She was unable to sit on the side of the bed due to rigidity. She died at age 89 and no autopsy was performed. She had a *FMRI* repeat size of 60.

2.3. Case 3

A 73-year-old woman presented with a five-year history of rest tremor in her right hand, difficulty with her balance, and micrographia. Her pedigree is in Fig. 1B. She was diagnosed with PD at age 70 by a neurologist who started her on carbidopa/levodopa. She had a robust response to the medication with resolution of her tremor. Quantitative scales were not performed. Brain MRI was unremarkable. At age 72, she developed worsening balance, general slowness, and problems with her short term memory. On examination, she had a mental state examination of 30/30, saccadic eye pursuits, masked facies, and oral buccal dyskinesias. Examination of her upper extremities showed cogwheel rigidity and bradykinesia with finger tapping and hand grasping. She had a stooped posture and a narrow based gait with decreased arm swing bilaterally. Her *FMRI* repeat size was 86.

2.4. Case 4

A 72-year-old right handed man presented with a 12-year history of tremor and slowing of his gait. His initial symptom was impaired balance, as he became unable to ride a bicycle and dance. He then developed frequent stumbling. At age 63, he developed tremor of his hands and was diagnosed with PD by a neurologist. Brain MRI was normal. He was started on carbidopa/levodopa and had a moderate improvement in his rest tremor, gait unsteadiness, and bradykinesia. Tolcapone and selegiline were added, but were not well tolerated. At age 68, he started to drag his left leg. His medical history included renal carcinoma leading to nephrectomy, impotence, and a fractured wrist. His pedigree is in Fig. 1C. Examination at age 72 showed normal cognition, masked facies, and hypophonic, raspy speech. He had rigidity and rest tremor in both extremities. Fine motor movements were bradykinetic. He had a mildly slowed gait, bilateral reduced arm swing, and retropulsion on the pull test. Tandem gait was normal. At that time, he was on carbidopa/levodopa three times daily with wearing off after 4 h. When the medication wore off, he experienced increased tremor, more problems with fine motor coordination, and balance difficulty. He denied dyskinesia but did describe vivid dreams. Pramipexole was added to his regimen with a mild improvement in rest tremor, bradykinesia, and gait. His *FMRI* repeat size was 64.

3. Discussion

Many features of these cases are similar to patients with idiopathic Parkinson disease. On initial description, men with FXTAS were reported to have neurological findings on the motor UPDRS, to include mild bradykinesia in 57% of patients, mild rigidity in 71%, and slight resting tremor in 40% [2]. Reduced facial expression, speech abnormalities, and postural instability were also increased compared to controls. A follow up cross-sectional case-control study confirmed these findings, with male *FMRI* premutation carriers having a parkinsonism subscore on the FXTAS rating scale twice as high as controls ($p = 0.0026$) [1].

Parkinsonism alone is not sufficient for a diagnosis of FXTAS based on proposed diagnostic criteria, which require intention tremor and gait ataxia [2]. These diagnostic criteria also required radiological findings, such as the ‘middle cerebellar peduncle sign’. The cases presented here would not meet criteria for FXTAS due to the lack of kinetic tremor and gait ataxia and normal brain imaging. However, these cases have features commonly associated with idiopathic PD, such as improvement with dopaminergic medications and dyskinesias.

Screening studies for the *FMRI* premutation in PD cohorts have not yielded many cases (0–1%), suggesting that the premutation does not account for a significant proportion of idiopathic PD [5–8]. In our PD cases ascertained through FXTAS studies, it is unclear if the premutation is causing the neurological signs or whether the presence of the premutation and PD is coincident. Due to the high percentage of FXTAS patients having parkinsonism in previous

studies, it is possible that the premutation is indeed causally associated. However, this case series is not sufficient to establish a causal link necessitating follow up studies to further investigate this issue. Because higher repeat size is correlated with earlier age of onset of the neurological signs in FXTAS [9], it is also possible that patients with low *FMRI* repeat expansions have not yet manifested FXTAS symptoms at the time of examination. The molecular basis of the parkinsonian features that occur in FXTAS is unknown.

Other cases of phenotypes not meeting criteria for FXTAS in *FMRI* premutation carriers have been reported. A parkinsonian patient with axial bradykinesia, hypophonia, and rest tremor was reported in a *FMRI* premutation carrier with 90 CGG repeats [10]. The patient did have kinetic tremor and a gait disturbance (not described as ataxia) and his symptoms improved on carbidopa/levodopa. Despite the presence of ubiquitinated nuclear inclusions in the cortex and hippocampus on autopsy which are characteristic of FXTAS, no Lewy bodies were seen. Loesch et al. also reported a patient with PD, motor fluctuations, and dyskinesia who was levodopa responsive and had a *FMRI* CGG repeat size of 81 [11]. A patient with characteristic FXTAS and a resting tremor of the jaw was reported to have both neuronal and astroglial intranuclear inclusions, in addition to Lewy bodies on autopsy [12]. However, it is likely that this patient may have had both FXTAS and idiopathic PD with his constellation of neurological signs.

Interestingly, a screening study of parkinsonism ascertained a *FMRI* premutation carrier who also carried a heterozygous *Parkin* mutation [13]. This patient clinically had Parkinson disease with an excellent response to carbidopa/levodopa, with onset at age 45. The authors suggest that the *FMRI* pre-mutation and the *Parkin* mutation may be susceptibility factors that contributed to disease in their patient. Our cases were not tested for *Parkin* mutations, but may warrant testing as it is unknown if gene–gene interaction or combinations of genes may increase risk for parkinsonism.

As has been the case with other genetic mutations in movement disorders, wider screening is leading to the expansion of potential neurological signs seen in associated with *FMRI* pre-mutations. Further research is required to define the spectrum of parkinsonian signs that are caused by *FMRI* premutations. Although data does not support screening PD patients for *FMRI* expansions, those PD patients with a family history of possible for known *FMRI* related disease, e.g. developmental delay, autism, premature ovarian failure, FXTAS, or fragile X syndrome warrant screening for the premutation and genetic counseling. The ramifications for other family members are significant. All daughters of premutation carriers males will be carriers themselves and are at high risk to have children with fragile X syndrome.

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Fig. 1. (A) Pedigree of Case 2. (B) Pedigree of Case 3. (C) Pedigree of Case 4. ◐ *FMR1* premutation carrier; ■ *FMR1* full mutation; ◑ *FMR1* premutation carrier with Parkinson disease; ◑ Parkinson disease; ◇ Unknown gender.